

Psychophysical Methods for the Measurement of Somatosensory Dysfunction in Laboratory Animals

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Somatosensory dysfunction is a widely reported clinical consequence of chemical exposure. Assessment of such dysfunction should be an important component of agent safety testing, necessarily implying evaluation of psychophysical functions in laboratory animals. The logic of testing agent-induced sensory dysfunction, conceptual and practical factors affecting such tests, and the categories of experimental methods available are reviewed.

Introduction

As Arezzo (1) has noted, the great length of the peripheral nerve fibers makes them exquisitely sensitive to neurotoxicants. Motor function mediated by the long fibers innervating the hind limbs is frequently affected early in cases of neurotoxicosis (2).

The peripheral nerve trunks carry both motor and sensory impulses, and sensory dysfunctions also are widely reported neurotoxic signs. Maurissen (3) has tabulated the array of agents, both drugs and toxicants, known to yield somatosensory dysfunction. Decreased vibration sensitivity, altered temperature sense, impaired tactile ability, numbness, and a variety of subjective effects have been seen clinically.

Clinical effects are human health consequences of agent exposure, surely a crucial component of the total environmental health research effort. More important, however, must be the prediction of human health risks of agent exposure and the elucidation of mechanisms of injury (4). We want to know what effects may occur in exposed human subjects, and by what means such effects occur,

without in fact exposing human subjects to potentially dangerous agents.

The general objective, then, is to demonstrate agent effects in nonhuman models, in the laboratory under controlled conditions of maintenance and exposure. Because the somatosensory systems are affected early by a variety of agents, assessment of somatosensory function requires a high priority.

I will review aspects of the broad problem of testing nonhuman subjects for agent-induced somatosensory dysfunction, discussing categories of somatosensory functioning; requirements for psychophysical assessment of sensory function; the logic of inferring agent effects on sensory functioning; and several general procedures for animal psychophysical testing.

Categories of Somatosensory Function

Any major textbook or reference source can be consulted for an overview of somatosensory function (5-8). A convenient summary groups functions by anatomical locus (Table 1). Within each grouping, subgroupings of phenomenal or subjective experience can be identified. Thus, the cutaneous senses include touch-pressure, temperature, vibration, and superficial pain.

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Table 1. Categories of somatosensory function.

Sense	
Skin senses	Touch-pressure
	Temperature
	Vibration
	Superficial pain
Deep senses	Muscle, joint, tendon sensation
	Deep pressure
	Deep pain
Visceral senses	Organic sensation
	(hunger, thirst, nausea)
	Visceral pain

Cutaneous sensitivity has probably been most extensively studied, because the locus to be stimulated is easily accessible. What follows here is oriented toward the measurement of cutaneous sensitivity exclusive of pain. [The psychophysics of pain is discussed elsewhere by Weiss and Laties (9).]

Despite the ease of access to the body surface, tests of cutaneous sensitivity are complicated by a range of factors beyond the magnitudes of physical stimulation applied. A simple example is the variability in sensitivity to two-point stimulation as a function of locus of stimulation (8): the tongue, for instance, is very sensitive, the back and thigh much less so.

Other factors modulate the phenomenal experience of cutaneous stimulation. Spatial patterning is implied directly in the measurement of two-point thresholds: two points of contact are experienced as one if the two points are sufficiently close together. Simultaneous spatially distinct contacts may have inhibitory, summatory, or other effects (7).

Temporal interactions also occur. Adaptation to prior or co-occurring stimulation (for example, different temperatures) may alter the subjective magnitude of stimulation.

Temporal and spatial patterning may interact. A tactile phi phenomenon (7), in which cyclic stimulation of two spatially distinct loci yields the experience of a single contact moving between the two sites, is well known. Neurologists take advantage of spatial-temporal patterning in tests of recognition of letters drawn on the skin and of objects by touch (8).

Intermodal effects among the cutaneous senses yield higher order experiences, as in "touch blends" (5). The experience of "oiliness," for instance, can be reduced to weak pressure plus warmth. The matching of objects examined tactually to samples presented visually is well known, even in non-human primates (10).

Kennedy (11), in a further interesting example of

higher order information available to skin senses, has reported that congenitally blind subjects are capable of identifying common objects depicted as raised ridges (the tactile equivalent of lines). Some blind subjects, asked to draw common objects, spontaneously invented line depiction conventions of interposition and linear perspective.

In summary, the experience of the environment available to the cutaneous receptors can occur on many levels, from those effects rather easily referred to the periphery to others which have complex cognitive components. Such effects pose challenging problems, and, in principle, any and all could be affected by exposure to toxic agents.

Characteristics of Psychophysical Assessments

In all the examples cited above, the issues are psychophysical ones. The general psychophysical problem is to discover the relation between some varying character of physical stimulation and variations in the experience of such stimulation. Physical stimulation is often multivariate (e.g., vibration varies in frequency and amplitude), so psychophysical assessments often yield families of functions.

Every psychophysical experiment involves three components. First, the characteristics of the physical stimulation must be carefully controlled. Control of stimulation requires attention to details of stimulus generation, calibration of stimulus-generating devices, and, often, monitoring of stimulation parameters during presentation. Second, the locus of stimulation must be specified, both the specific body part and the extent and/or shape of the area stimulated. Locus is particularly important when repeated tests of function are intended, as across days, weeks, or months. Third, a means by which the subject can report his/her experience of the stimulation must be provided. Reports can range from very simple (a switch closure or a yes-no verbal report) to very complex (an introspective description).

Procedural details go beyond these three major components. The order of presentation of stimuli, their context (e.g., background or adaptation stimulation), and the kinds of comparisons to be reported all affect the design of particular investigations. Engen (12) provides a concise survey of these issues.

All three of the major components listed pose difficulties for psychophysical assessments in animals. Perhaps the biggest hurdle is the requirement for a response mode that can vary with changes in stimulation. At best, one can get a crude

categorical response (on the order of low-medium-high, or yes-no-not sure) from the animal, and most frequently investigators settle for some form of a yes-no response. Even so, guaranteeing that the response is being made appropriately, to the aspect of stimulation of interest and not to extraneous cues (e.g., apparatus noises) may require extensive preliminary training and/or a variety of control tests (13). The training investment, on the other hand, may purchase exquisite precision in the control of responding by the stimuli of interest.

Control of the locus of stimulation with human subjects is a relatively minor difficulty because we can enlist the subject's cooperation via verbal instructions. The animal subject either must be trained to maintain an orientation toward stimuli, be restrained in some manner, or both, in order that stimulation can be reliably applied to a specifiable body locus.

Always, precisely describable stimuli must be generated. The emergent problem here is that, in animal psychophysics, automation of the stimulus presentations, their order and variations, is desirable. The additional equipment required may increase the cost and complexity of animal psychophysical study.

Assessment of Agent Effects on Sensory Systems

In general, a sensory dysfunction can be inferred from the observation that the psychophysical function for an agent-exposed subject is displaced relative to, or of a different shape than, the corresponding function in a nonexposed subject. Such evaluations are multivariate: while response change (or some derived measure, such as probability of response) is the single dependent variable, independent variables may include the parameters of the stimulus of interest (e.g., frequency and amplitude), yielding a family of curves, and must include a range of doses of the agent in question. Results reviewed by Stebbins and Moody (14) illustrate these points.

Since we infer altered sensory function from altered response, it is critical that nonsensory explanations for altered response be ruled out. Peripheral neuropathies, as a case in point, yield motor as well as sensory signs. Since some psychophysical procedures used with animals manipulate motivational levels (via food or water deprivation), and since ingestional changes often occur in toxicosis, motivational changes must be considered as a possible factor in response alterations.

Finally, modern psychophysical thinking invokes

the concept of response bias, referred to an internal criterion for reporting detection of stimulation. Estimation of response bias is a central aim of signal detection theory (15). Signal detection methodology has been extended to the analysis of animal psychophysical studies in a number of cases. In principle, an effect of toxic agents may be to shift the subject's response criterion, an effect that would be reflected as a change in response bias, while detectability of the stimulus may or may not be affected.

Overview of Animal Psychophysical Techniques

A variety of sources on animal psychophysical methods are available, with extensive bibliographies (13, 16, 17). My aim here is to critically review some of the available techniques for their usefulness in assessing agent-induced sensory dysfunction. The principal context is the evaluation of somatosensory function, but it must be stressed, on the one hand, that there are very few apparent applications of any of these methods in the somatosensory domain and, on the other hand, that any of these methods could probably be applied to any sensory modality, given some ingenuity. Restrictions on applications are logistical and engineering problems rather than conceptual ones.

The overview presented here is summarized in Table 2, where candidate procedures are rated against major considerations in choosing a technique.

Factors in Evaluating Animal Psychophysical Methods

Factors Related to the Psychophysical Function

There are three such factors: control of the parameters of the physical stimulation; control of the body locus, or sensory organ, stimulated; and the precision of the psychophysical function(s) that can be obtained. The first two have already been discussed. The precision of the psychophysical function refers to the degree of variability resulting from any of a number of sources, perhaps the greatest of which is the "tightness" of the association between stimulus and response. Some methods are intrinsically more variable; others may provide for exquisite control of responding by stimulation.

Table 2. Comparison of animal psychophysical procedures.

Factors affecting choice	Method ^{a,b}						
	1	2	3	4	5	6	7
Control of stimulation parameters	0	+	0	-	+	+	+
Control of locus of stimulation	0	+	0	-	+	+	+
Precision of psychophysical function	-	+	0	-	+	+	+
Sensory-motor separation	-	0	+	-	+	0	0
Possibility of, need for response bias measurement	+	+	+	-	+	0	0
Motivational manipulation required	+	+	+	+	+	-	-
Amount of response training required	+	+	+	+	+	-	-
Amount of testing time required per function	-	+	-	-	+	0	-
Repeatability across time	+	+	+	+	+	+	+
Applicability to neonates	+	+	+	-	+	0	0
Labor intensiveness	-	0	0	0	0	+	+
Automatability	-	+	0	0	+	+	+
Equipment cost, complexity	+	0	0	+	-	-	-

^aMethods are rated as follows: (+) advantage; (-) disadvantage; (0) no clear advantage or disadvantage.

^bMethods are as follows: (1) reflex, orientation, or forced movement (kineses) measures; (2) reflex modulation; (3) habituation/dishabituation; (4) preference, tropism measures; (5) classical conditioning; (6) operant conditioning; (7) conditioned suppression.

Factors Related to Alternative Explanations for Altered Psychophysical Functions

Three factors (separation of sensory from motor components; response bias; and altered motivational milieu) have been discussed above. Psychophysical methods differ with respect to the degree that sensory and motor components of observed response change can be controlled or measured or come into play. Some methods, for instance, may utilize autonomic response: thus, the motor component is negligible. In other cases, responses to varying stimuli may be evaluated as relative to one another; altered motor components, if they are homogeneous across the stimulus range being tested, may be taken out of consideration.

Response bias in some sense is an analytical entity. That is, under appropriate experimental designs, it can be evaluated separately from detectability. Blough (18) provides an example of how such analyses can be performed. A range of designs lend themselves to response bias evaluation and the possibility of doing so is of some advantage.

Factors Related to Logistics and Design of Experiments

A prime motivation for listing this set of factors is that a large number of agents stand in need of some testing (19). Consequently, the time required to train and test subjects is an important consideration. Since dosing regimes that simulate environmental exposures are typically chronic and since

the effects may be expected to be cumulative, methods that are repeatable across time (within-subjects designs) are most useful. Given the continuing strong interest in the evaluation of pre- and perinatal exposures, methods applicable (at least in principle) with very young organisms would be especially useful.

Economic Factors

No laboratory has infinite resources. Therefore, cost factors inherent in any method must be taken into account. The labor intensiveness and the level of such labor (e.g., kind and amount of training required) affect costs. Some methods may be automated, at some cost for development and for equipment, balanced off against labor costs saved, precision obtainable, and the possibility of testing more animals per unit of labor.

Candidate Procedures in Animal Psychophysics

Reflex, Orientation, and Forced Movement (Kineses) Measures

Reflexes are "prewired" motor or autonomic responses to stimuli, usually of a limited sort applied to a limited body region; the neurology literature provides numerous examples. Orientation measures refer to movements directed toward stimuli; these may be at a distance (sound, light, or chemical source) or on the body surface (a tactile stimulus

Environmental Health Perspectives

applied to the skin). Kineses (20) refer to increases in activity as a function of imposed stimulation, e.g., increased movement at higher temperatures. Rough psychophysical functions can be derived by observing the variations in probability, amplitude, and/or latency of any such response as stimulus parameters are changed (19, 21).

The major advantages of such methods are that, since the responses are built in, no training or motivational manipulations are necessary, and response bias is not a problem. Tests can be repeated in the same animals across time, so long as short-term effects (habituation) are allowed for. In principle, where appropriate reflexes can be identified, these methods should be applicable to neonatal animals. Equipment costs will probably be low.

The principal disadvantage is that, since reflexes are by definition sensory-motor arcs, sensory components may not be separated easily from motor effects. The functions obtained may be relatively imprecise, and the amount of hand labor required to derive functions may be quite large. These procedures are not readily automated.

Reflex Modulation

Hoffman and Ison (22) point out that the magnitude of a reflex (for instance, a startle response to a sharp noise) can be depressed by precedent or co-occurring stimuli, and that the reflex inhibition is related to the detectability of the precedent stimulus. This prepulse inhibition of reflexive response obviously can be incorporated into a psychophysical experiment. Russo (23) has reported the successful use of this technique to detect sensory dysfunction induced by environmental agents.

Reflex modulation holds great promise as a method for assessing agent-associated sensory dysfunction. Control of stimulation can be excellent, both in location and parametrically. The functions obtained (23) can be quite precise. Because the method is reflexive, response bias is not a problem and no motivational manipulation is required. Also, no special response training is necessary and the evaluation can be repeated across time. The method is useful with neonates (24) and can be automated, in at least some applications.

Habituation/Dishabituation

Presentation of a novel stimulus frequently can be seen to produce an orienting response, with both motor (startle) and autonomic (e.g., heart rate change) components (25). With repeated presentations, the orienting response wanes (habituation). Presentation of a second stimulus following habituation to

the first may reinstate the orienting response (dishabituation). The habituation/dishabituation paradigm may be used as a psychophysical method.

An example of this approach is the work of Moffitt (26), who found that very young human infants could discriminate small speech sound differences. Infants showed habituation of a heart rate change to the syllable "ba" and dishabituation to a second syllable, "ga", which differed in one phoneme from the first.

Habituation/dishabituation has the advantage of potential for separating sensory from motor effects of toxicants, in that autonomic measures can be used. This supports the method's use with neonates, too, where motor control may not be well developed. In fact, the method might be usable with some organisms prenatally. As with other reflex measures, response bias is not likely to compromise inferences of sensory dysfunction.

The major drawback is the amount of time likely to be required to derive a psychophysical function. Since the method employs (multiple) paired comparisons, testing may be quite time consuming.

Note that failure to observe dishabituation does not allow the inference of non-discriminability of stimuli. Observation of dishabituation, however, is clear evidence for discriminability.

Preferences and Tropisms

Most organisms have multimodal preferences for a sensory context and, given the opportunity, will spend more of their time in the preferred context. For some organisms and some stimuli, the movement toward or away from the source of stimulation (e.g., heat, a chemical source) is highly reliable and predictable on the basis of knowledge about the gradient of stimulation present (20).

A typical preference experiment employs a choice box of some sort in which stimulus characteristics differ in two regions. By recording the relative proportion of time spent in the two areas, a rough psychophysical function can be generated.

In approximately the same fashion, tropisms may be tested: in this case, a gradient is constructed. For instance, a metal plate with one hot and one cold end specifies a temperature gradient. By noting the proportion of time spent in various zones of the gradient, again, a rough psychophysical function can be plotted.

These approaches have the advantage of relative simplicity. It is possible to automate them, for example, by using photocell arrays along a runway. Equipment cost and complexity generally will be low. Because the procedures depend on built-in preferences, no motivational manipulations are nec-

essary and no special training is required. The method should be repeatable across time, too.

Control of the locus of stimulation will be difficult because the animal controls its own stimulation. The amount of time required to determine a psychophysical function may be protracted. The methods may be labor intensive, but the observations probably do not require a high degree of technical skill.

Since locomotor responses are typically employed, sensory and motor components will probably be confounded. Response bias (vs. detectability) is not obviously measurable. As with habituation/dishabituation, absence of preference does not necessarily imply absence of discriminability.

Classical Conditioning

Classical conditioning can be used effectively in psychophysical experiments. The general procedure is to pair a signal, called the conditioned stimulus (CS), with an unconditioned stimulus (UCS), often mild electric shock. Usually the CS precedes or overlaps the UCS. The UCS elicits an unconditioned response or reflex (UCR), which may be overt, as a limb flexion, or covert, as a heart rate change. After some number of CS-UCS pairings, the CS alone comes to elicit a response like that elicited by the UCS. The response to the CS is called a conditioned response or reflex (CR). The ability of a stimulus to become a CS⁻ is *prima facie* evidence for its detectability.

Discriminative responses can also be established, in which case one stimulus is a CS⁺, paired with the UCS, and another is a CS⁻, paired with the absence of the UCS. By manipulating the difference between CS⁺ and CS⁻ pairs, their discriminability can be tested. Thus, measurement of thresholds for stimulus differences is possible.

Examples of classical conditioning in broadly psychophysical contexts are easily found in the psychology literature of the past century. Some recent applications that illustrate the potential of classical conditioning can be seen in the work of Kreithen and colleagues (27). The general problem Kreithen addresses is to discover the possible sensory bases for homing in pigeons.

His procedure is relatively straightforward. Stimuli of interest (the CS) are paired with mild subcutaneous electric shock (UCS) while heart rate is monitored. Heart rate acceleration (UCR) reliably follows shock. If the CS is detectable, it comes to elicit a heart rate acceleration. Conditioning is reported to occur after about 10 CS-UCS pairings; the remainder of a 50-trial session can then be devoted to varying stimulus parameters, during

which a reliable psychophysical assessment can be made.

Using this procedure, Kreithen has studied sensitivity to magnetic fields, to barometric pressure changes, to the plane of polarized light, and to very low frequency sound (infrasound).

The only obvious disadvantage in this procedure is that equipment for recording and control of stimulus presentations may be relatively complex and expensive, but classical conditioning promises to be advantageous on most of the other factors listed.

Parenthetically, classical conditioning procedures are major components of Soviet behavioral toxicological assessments (28), and are reported to be very effective in demonstrating neurobehavioral toxic effects.

Operant Conditioning

The methodology of operant conditioning in psychophysics is reviewed elsewhere (13, 16, 17, 29). Operant procedures have been the most widely applied methods for the precise definition of animal psychophysical functions, for many reasons: The test apparatus can be tailored to the animal under test such that excellent control of stimulus parameters and locus of stimulus application are possible. The timing, location, type, frequency and ultimate control of responding, coupled with the control of stimulation, can lead to extremely precise psychophysical functions. Functions have been shown to be highly repeatable across relatively extended periods of time. Operant methods have developed as highly automated technologies over the years; automation reduces labor costs but generally increases complexity of equipment and equipment costs.

Major disadvantages of operant procedures include the frequent requirement of motivational manipulation (e.g., food deprivation) and the fact that stable responding may only follow very extensive training.

Excellent examples of operant psychophysical methods in the somatosensory domain can be seen in the work of Maurissen (3), who is studying detectability of vibratory stimuli in monkeys, and in the approach reported by Burne and Tilson (30). The latter employ a relatively high probability response in restrained rats, a nose poke that is sensed by a photobeam interruption. Step-wise shock level changes are applied to the rat's tail, incrementing on a fixed-time schedule and decrementing contingent on the response. By monitoring the shock level increment-decrement reversals, the rat's threshold for reactivity to electric shock can be tracked.

The presentation of stimulation by itself can be a reinforcing event (31). In principle, this could be a

foundation for psychophysical evaluation; it resembles the preference method mentioned earlier, with similar advantages and disadvantages.

For some purposes, the precision that can be obtained using operant methods may far outweigh the disadvantages. If, for example, correlations between histopathological changes and functional disruption are the objective (14), the results achievable may justify the expense and time. At the other extreme, operant psychophysics may be prohibitively expensive for agent screening ends, at least as such methods are currently known. Given the flexibility operant methods have demonstrated over the years, it may be that ingenious screening applications can be found in the operant psychophysical domain.

Conditioned Suppression

The operant and classical conditioning approaches have been combined in the conditioned suppression method. Animals trained under an operant schedule of reinforcement to emit a stable and moderately high rate of responding are exposed to a signal (CS) which precedes an unconditioned stimulus (UCS), often mild electric shock. Responding is interrupted, suppressed, by the UCS; thus, suppression of response can be considered an unconditioned response. Over some number of CS/UCS pairings, the CS comes to suppress responding. Suppression of responding from a stable baseline in the presence of a CS then is evidence for detectability of the CS.

Typically, suppression is expressed as a ratio between pre-CS responses and CS responses, often calculated so that it can vary between 1.00 (complete suppression) and zero (no suppression). The suppression ratio increases toward 1.00 as conditioning progresses and varies directly with the detectability of stimuli. Applications of conditioned suppression to detectability problems have been reviewed by Smith (32) and have been used successfully in a variety of modalities, including cutaneous sensitivity.

Given that conditioned suppression is a hybrid operant-classical conditioning method, it tends to suffer from the disadvantages of both. Particularly, training and testing time, overall, may be excessive, and equipment may be relatively complex and expensive. The operant baseline will generally require a motivational manipulation, though the suppression of responding itself will not.

Since the suppression ratio should be relatively insensitive to baseline shifts from session to session, the psychophysical functions derived should be relatively invariant, except for induced sensory changes.

Summary and Conclusions

The investigator interested in assessing agent-induced sensory function changes has a rather broad inventory of methods at his disposal. In general, selection of any psychophysical method entails trade-offs, most frequently perhaps the precision-cost balance, where cost includes time, equipment, and labor expenditures. Simple, manual, quick procedures tend to yield imprecise psychophysical functions; more complex, automated, time-consuming techniques may lead to exquisitely precise functions.

A survey of animal psychophysical studies would demonstrate a preponderance of effort on the visual and auditory systems. Other modalities, from the familiar (taste, olfaction) to the exotic (barometric pressure, magnetic field sensitivity, sensitivity to electrical fields) have also been examined from time to time. The facile generalization is that it is easy to think in terms of the familiar modalities; those that are of less apparent immediacy to human life inspire less interest. However, where the interest exists, it seems that available psychophysical procedures (with some ingenuity) can be brought to bear.

The somatosensory domain is one of those in which animal psychophysical study has been relatively neglected. Maurissen's survey (3) of the overwhelming prevalence of agent effects on somatosensory function argues persuasively that the time is at hand to reverse this neglectful trend. For unknown agents, if they affect the nervous system at all, disruption of peripheral somatosensory function seems always to be a safe prediction.

Consequently, there is an immediate urgent need for the application of existing animal psychophysical methods to the somatosensory area and for innovative new approaches, particularly where time and cost advantages can be found.

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